

Citation for published version:

Hamann, P, Holland, R, Hyrich, K, Pauling, JD, Shaddick, G, Nightingale, A & McHugh, N 2017, 'Factors associated with sustained remission in rheumatoid arthritis in patients treated with anti-tumour necrosis factor (anti-TNF)', *Arthritis Care and Research*, vol. 69, no. 6, pp. 783-793. <https://doi.org/10.1002/acr.23016>

DOI:

[10.1002/acr.23016](https://doi.org/10.1002/acr.23016)

Publication date:

2017

Document Version

Peer reviewed version

[Link to publication](https://doi.org/10.1002/acr.23016)

This is the peer reviewed version of the following article: Hamann, P. Holland, R. Hyrich, K. Pauling, J. D. Shaddick, G. Nightingale, A. Mchugh, N. (2016) Factors Associated With Sustained Remission in Rheumatoid Arthritis in Patients Treated With Anti-Tumor Necrosis Factor. *Arthritis Care and Research*, 69(6), which has been published in final form at <https://doi.org/10.1002/acr.23016>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

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Accepted for Publication in Arthritis Care and Research 9th August 2016

Available online at:

<http://onlinelibrary.wiley.com/doi/10.1002/acr.23016/abstract;jsessionid=2E8C78220DDC9CF166F7478FBEB2B7CA.f03t03>

Citation:

Hamann, P., Holland, R., Hyrich, K., Pauling, J. D., Shaddick, G., Nightingale, A. and McHugh, N. (2016), Factors Associated with Sustained Remission in Rheumatoid Arthritis in Patients Treated with Anti-Tumour Necrosis Factor (anti-TNF). Arthritis Care & Research. Accepted Author Manuscript. doi:10.1002/acr.23016

Factors Associated with Sustained Remission in Rheumatoid Arthritis in Patients Treated with Anti-Tumour Necrosis Factor (anti-TNF)

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Financial Disclosure Statement:

Professor Hyrich has received honoraria of less than \$10,000 from Pfizer and Abbvie. None of the other authors have any conflicts of interest to declare.

Abstract

Objectives. Anti-tumour necrosis factor antibody (anti-TNF) has revolutionised the treatment of rheumatoid arthritis (RA) and remission is now a realistic possibility for patients. Despite widespread use of anti-TNFs, predicting which patients are most likely to attain a sustained good response to these treatments remains challenging. Our objective was to undertake a systematic review of the literature to evaluate existing evidence for demographic and clinical factors associated with the achievement of sustained remission in individuals with RA treated with anti-TNF.

Methods. EMBASE, MEDLINE and the Cochrane Controlled Trials Register were searched along with studies identified from reference lists. Quality of studies was assessed using Newcastle-Ottawa criteria. Meta-analysis was undertaken where unadjusted odds ratios were available for the same demographic or clinical factors from at least three studies.

Results. Six studies were identified. Concomitant methotrexate use was associated with an increased likelihood of achieving sustained remission. Greater baseline disease activity, tender joint count, age, disease duration, baseline functional impairment and female gender were associated with reduced likelihood of achieving sustained remission.

Conclusions. Factors predicting sustained remission are seldom reported. Evidence identified in this review supports current recommendations for methotrexate co-prescription and highlights the negative impact of

particular clinical and demographic features on the likelihood of achieving optimal response to anti-TNF treatment. Sustained remission is clinically more relevant than point remission in RA. More widespread reporting of sustained remission will help clinicians set realistic expectations on likely long-term treatment efficacy and could be an important tool for identifying patients suitable for dose optimisation.

Significance and Innovation

- Demographic and clinical features can help to predict sustained remission with anti-TNF.
- Female gender is associated with a reduced likelihood of achieving sustained remission.
- Methotrexate co-prescription with anti-TNF is associated with an increased likelihood of achieving sustained remission.

Aggressive treat-to-target strategies, alongside increased use of biologic agents such as anti-tumour necrosis factor antibody (anti-TNF)(1,2), have improved outcomes for patients with rheumatoid arthritis (RA) and the aim of achieving sustained remission is a realistic aspiration.

Response to anti-TNF, however, remains variable and requires further investigation. Waiting to assess efficacy of anti-TNF is time-consuming, often taking months for clinicians and patients to identify that the treatment is not working, and can be frustrating if anticipated clinical improvements do not materialise. Unsuccessful trials of anti-TNF therapy in RA also have important healthcare cost implications. Understanding how the demographic and clinical features of a patient may influence the likelihood of achieving sustained remission with anti-TNF will help physicians personalise treatment strategies and might enable patients to achieve sustained remission sooner through early choice of drug that offers the best likelihood of success.

The majority of published studies report remission rates at a single time point, or sequential point remission rates. It may be unclear whether the proportion of patients identified in remission at sequential time points are the same patients, or are a varying group of individuals, with some patients moving in and out of remission over time. European League Against Rheumatism (EULAR) guidance (3) recommends achieving remission as early as possible with consideration of tapering anti-TNF agents if sustained remission is achieved, and Outcome Measures in Rheumatology (OMERACT) define the duration of sustained remission as six months (4). Previous systematic reviews have only investigated predictors of point remission in RA (5), however, given the chronicity of a condition such as RA and the long-term benefits of remission, a durable positive response to anti-TNF is a more clinically relevant outcome.

Our objective was to undertake a systematic review of the literature to evaluate the existing evidence for demographic and clinical factors associated with the achievement of sustained remission in individuals with RA treated with anti-TNF.

Patients and Methods

The systematic review protocol was registered prospectively with the PROSPERO database (<http://www.crd.york.ac.uk/PROSPERO/>, reference CRD42015015983). PRISMA-P (6) and PRISMA (7) recommendations were followed in the development and implementation of the review.

Inclusion criteria

To be included in the review, papers had to meet the following criteria:

- 1) Phase three or four clinical trials, long-term extension trials or cohort studies reported as original research in the form of journal papers;
- 2) Adults (≥ 18 years of age) with RA according to ACR 1987 (8) or ACR/EULAR 2010 (9) criteria;
- 3) Report on anti-TNF used for the treatment of RA;
- 4) Report on at least one measure of RA disease activity using DAS (10), DAS28 (11,12), CDAI (13), SDAI (14), ACR/EULAR remission (15) or ARA 1981 remission criteria (16);
- 5) Report on predictors of sustained remission (at least six months) (4).

Exclusion criteria

Studies where it was not possible to isolate the required data on patients in sustained remission, case-control, cross-sectional studies, case reports/series, phase one and two/laboratory studies, qualitative studies, survey-based studies, narrative reviews, conference abstracts and editorials were excluded.

Search methods for identification of studies

EMBASE, Medline and the Cochrane Controlled Trials Register were searched using the Ovid platform to 4th September 2015. The full search strategy for Medline is provided in supplementary online table 1. No language restriction was applied to search results. Reference lists of included studies were searched for additional citations and all authors were contacted for additional information to assist with the review and meta-analysis. Additional data were kindly provided by Dr Barnabe, Dr Einarsson, Dr Balogh, and Professor Tanaka.

Assessment of studies for inclusion in the review

All search results were dual screened with dual data extraction and quality scoring using a custom Access™ database. The quality of studies was assessed using the Newcastle-Ottawa Scale(17). A narrative review of studies with relevant quantitative data extraction was undertaken. Corresponding authors were contacted to obtain unadjusted data to enable meta-analysis where appropriate. Sources of heterogeneity were investigated through structured critical appraisal.

Meta-Analysis

Statistical analysis was undertaken using Review Manager Software version 5.3(18). Because the factors incorporated in calculating adjusted odds ratios (OR) were not consistent between studies, unadjusted OR were used in meta-analysis where data were available from at least three studies. A random effects model was used to allow for between study variation. Heterogeneity between studies was assessed using I^2 (19) and publication bias was assessed using funnel plots.

Results

Study identification

4438 papers were identified from the search strategy. 4220 records were excluded and 218 full text papers, including 50 randomised controlled trials, were assessed. Six papers met the inclusion criteria and were included in the review (20-25). One of these papers (24) had included one patient aged less than 18 years old in one subgroup (personal correspondence), however, the mean age of all the subgroups and the overall cohort was in line with the other included papers, and it was decided to include the study in the review. The screening process is summarised in Figure 1.

Study design

The characteristics of the included studies (and quality assessed using Newcastle-Ottawa scores) are summarised in Tables 1 and 2. Two of the included studies were multicentre studies (23,24), coordinated from one hospital, one of which was an open label, non-randomised trial(23). One study was a retrospective case note review (26) and three were registry studies (20,21,25).

Sources of Heterogeneity

All studies included in this review were observational by design and therefore there was variation in the range of treatments and patients included. Neither of the two multicentre studies (23,24), or the retrospective case note review (26) described their selection criteria and therefore there is a potential for the introduction of bias. Three of the included papers were registry studies (20,21,25) and are more likely to be representative of the general RA population treated with anti-TNF.

Definitions of sustained remission utilised

The definitions of sustained remission varied across the included studies. The minimum length of time that different studies defined sustained remission, varied from at least six months, to nine months, or 'two consecutive visits' (verified to be at least six months (27)); and a range of outcome measures (DAS28, CDAI, SDAI, ACR/EULAR criteria) were also used. Additionally, Einarsson et. al. (25) did not exclude patients who were in a state of sustained remission who had a single episode of increased disease activity. However, it was less clear how the other studies handled these cases.

Missing data

The extent of missing patient data in sustained remission was not clear in the study by Balogh et al. (24); and detail on 25% (seven patients) of the cohort in sustained remission was missing from the study by Brocq et al. (22) which meant that data from these studies could not be included in meta-analysis. A total of 46 patients (1.9%) were lost to follow-up in the study undertaken by Einarsson et. al. (25), and last observation carried forward and LUNDEX correction was used to account for incomplete follow-up visits (28). Barnabe et al (20) and Furst et. al. (21) did not use imputation, but did not give any information on missing data. Last observation carried forward was used to impute missing data in the HONOR Study (23).

Achievement of sustained remission

There was wide variation in rates of sustained remission. The highest rate of DAS28 sustained remission was in the HONOR study (23) (38.1%), and the lowest rate of DAS28 sustained remission was noted in the CORRONA population (21) (7.9%).

Anti-TNFs and concomitant medications studied

The studies identified in this systematic review include a range of anti-TNF medications. Some studies (20,22,23,25) specifically reported which anti-TNFs were studied, whereas the studies by Furst et al.(21) and Balogh et al. (24) did not. Very little data was available for patients using the newer anti-TNF medications (certolizumab pegol and golimumab), and no data were available for biosimilar anti-TNF medications. Additionally, the use of concomitant allowable drug use (such as prednisolone and NSAIDs) differed between included studies (Table 2).

Despite these differences, there were many similarities in the baseline demographics, including mean age, gender, and concomitant synthetic disease modifying anti rheumatic drug (DMARD) use (Table 2) suggesting that although there is likely to be heterogeneity between studies, there are sufficient similarities to allow comparison between studies.

Impact of patient demographics on sustained remission

Gender. Female gender was negatively associated with DAS28 sustained remission in two of the studies (21,25) (Table 3). In contrast, Barnabe et al. did not find female gender to be significantly associated with sustained remission by DAS28, ACR/EULAR 2011, or SDAI criteria using multivariate modelling, although univariate analysis (personal communication; univariate analysis used in meta-analysis) did suggest an association. No association between sustained remission and gender was identified by Tanaka et al. (23), and was not reported by the remaining studies (22,24). Meta-analysis demonstrated a reduced likelihood of achieving sustained remission in females compared with males with low data heterogeneity and a low likelihood of publication bias (Figure 2).

Age. Increasing age was negatively associated with sustained remission by DAS28 in three of the studies (21,24,25) but was not associated with sustained remission in the study by Tanaka et al.(23) and was not

reported by the remaining studies (20,22). Uniform unadjusted data were not available for this variable to enable meta-analysis.

Obesity. The only study to report the relationship between obesity and sustained remission identified a negative association according to ACR/EULAR Boolean criteria excluding the CRP, but not by the other remission criteria included in the study (20).

Impact of disease characteristics on sustained remission

Baseline disease activity. Higher baseline disease activity was associated with a reduced likelihood of achieving sustained remission using the DAS28 score (21,23,25) and CDAI (21). No association was noted between baseline disease activity and subsequent sustained remission in the multivariate analysis by Barnabe et al. (20). The association between baseline disease activity and attainment of sustained remission was not reported in the remaining studies (22,24).

Patient Global Score. A lower baseline patient global score was associated with sustained remission in the HONOR study (23). However, the only other study to include patient global scores did not identify any association (20).

Acute phase reactants. An elevated erythrocyte sedimentation rate (ESR) was negatively associated with sustained remission in the HONOR study (23), but not in the study by Barnabe et al. (20). The C-reactive protein (CRP) did not predict sustained remission in the two studies where it was reported (20,25).

Number of tender and swollen joints. A greater number of tender joints negatively predicted sustained remission by CDAI criteria (20) and DAS28 criteria (24). However, no association was identified by Tanaka et al. (23). A higher swollen joint count was not identified as being associated with sustained remission in any of the four studies that reported this data (20,21,23,24).

Functional impairment. Higher rates of patient-reported functional impairment at baseline (assessed using the Stanford Health Assessment Questionnaire; HAQ) were consistently associated with lower rates of sustained remission (21,23,25). Only one study did not identify an association between baseline HAQ score and sustained remission on multivariate analysis (20). The effect of baseline functional impairment on remission status was not reported in the remaining studies (24,26).

Disease duration. One study identified that increased disease duration (stratified into five-yearly increments) was associated with a decreased likelihood of achieving sustained remission with the CDAI but not DAS28 criteria (21). Shorter disease duration was associated with an increased likelihood of achieving sustained DAS28 remission in one study (23). The remaining studies either found no association (20,25) or did not report on the association between disease duration and sustained remission (22,24).

Early response to treatment. Response at 16 weeks after treatment was only reported by one study (20) and was associated with an increased likelihood of achieving of sustained remission by DAS28 criteria.

Concurrent and Past Medication Use

Methotrexate. Concomitant methotrexate use was positively associated with sustained remission by DAS28 criteria (21,25) and CDAI (21). However, Tanaka et al. (23) did not find any significant difference in baseline methotrexate dose between the sustained and non-sustained remission groups.

Prednisolone. Prednisolone use was negatively associated with sustained CDAI but not sustained DAS28 remission in one study (21). However, no association was identified in the study by Einarsson et al. (25). Prednisolone use was restricted to a stable dose of less than 5mg in one study (26) and patients taking concomitant corticosteroids were excluded from two studies (20,23). The remaining study did not report corticosteroid use (24).

Prior anti-TNF use and Efficacy. Furst et al.(21) was the only study to report data on prior anti-TNF use and found that this was negatively associated with sustained remission in both DAS28 and CDAI measurements. Einarsson et al.(25) investigated time to sustained remission for each anti-TNF and found that etanercept was associated with an increased likelihood of achieving sustained remission within the first twelve months on treatment when compared with infliximab.

Discussion

Despite the variability in both the definition of sustained remission, and the predictive factors reported by each study, some common themes have emerged. One of the most striking findings was the paucity of evidence available for factors associated with sustained remission as an outcome. From over 4000 possible manuscripts identified in the search, only six studies were identified which met the inclusion criteria, all of which were observational. With the exception of one study (23), only 4.5% - 15.8% of patients were identified as being in sustained remission in any of the studies.

A number of clinical factors including increased disease duration, higher baseline disease activity score, increased baseline tender joint count, and a greater baseline functional impairment are associated with a reduced likelihood of achieving sustained remission. Demographic factors that appear to be negatively associated with sustained remission include female gender and increasing age. Only one clinical factor (methotrexate co-prescription) was associated with an increased likelihood of achieving sustained remission in more than one study. Supporting these findings, Katchamart et al. also identified these factors as predictors of point remission in a systematic review (5). Interestingly, the rates of sustained DAS28 remission identified in this review (7.9 – 38.1%) compare favourably with the range of point DAS28 remission rates (5 - 40%) identified by Katchamart et. al. However, the studies identified by Katchamart et.al. included both biologic and synthetic DMARD treated RA patients enrolled in studies between 1999 to 2008. By comparison, this review focused on anti-TNF treated patients only, and the oldest study in this review dates from 2009.

Our review identified that female gender appears to be strongly associated with a reduced likelihood of achieving sustained remission in two of the included studies. However, female gender has been associated with a higher baseline ESR in a normal 'healthy' population compared with males, and is also known to increase with

age (29). Given ESR is a component in the DAS28-ESR, it is possible that variations in gender and age may be confounders in the interpretation of the score which does not have different thresholds for these factors, rather than being true predictors of poor response. This may explain why Furst et al.(21) identified that female gender was associated with a lower likelihood of achieving sustained remission when using DAS28-ESR criteria, but not when using CDAI (which does not include an inflammatory marker component).

The finding that both increasing age and longer disease duration are both associated with a reduced likelihood of achieving sustained remission is unsurprising, and further studies are required to ascertain the independence of these effects. An important finding is the impact of baseline functional impairment on likelihood of achieving sustained remission. However, it remains uncertain whether worse functional impairment is a true predictor of response, or acting as a proxy marker of recalcitrant higher disease activity, irreversible joint damage, pain or fatigue, which may not be responsive to anti-TNF.

The only intervention that was associated with an increased likelihood of achieving sustained remission was methotrexate co-prescription. Whilst there may be alternative causal pathways that are responsible for this association (e.g. confounding by indication arising from the differing tolerance of methotrexate between patients), and it is difficult to assess cause and effect pathways using solely observational data, this association does appear to support the practice of co-prescription of methotrexate with anti-TNF wherever possible(30).

There was an absence of any comorbidity data in the included studies. Furst et. al.(21) and Einarsson et al (25) both describe collection of comorbidity data, however no analysis was reported. None of the other studies included any reporting on comorbidity data. The association between RA and increased cardiovascular risk is well documented (31), as is the apparent risk reduction in RA patients successfully treated with anti-TNF (32). However, this review did not identify any evidence on cardiovascular outcomes in RA patients achieving sustained remission with anti-TNF.

Interaction between predictors and outcomes is challenging when using composite score outcome measures, particularly when variables included in the score are also identified as a predictor of that score. All the disease activity outcome measures used in RA are composite measures, and some of the predictors identified in this

review, and the review by Katchamart et al. (5), are also components of these scores. An example of this is the association between higher baseline tender joint count and reduced likelihood of achieving sustained remission. It is unknown if having more tender joints prior to starting anti-TNF is a negative predictor of achieving sustained remission, or whether there is interaction with the composite outcome measure, within which tender joint count comprises a component. This review also identified that higher baseline disease activity was negatively associated with the likelihood of achieving sustained remission; although this association may be on the causal pathway in the relationship between tender joint count and sustained remission. It is possible that composite disease activity scores may not be efficient at measuring reduction in inflammatory burden. Due to the multifaceted nature of a composite outcome measure, non-inflammatory components (such as the global health measure) may reduce the sensitivity in detecting the change in inflammatory activity achieved by anti-TNFs.

A surprising finding was that no objective clinical measure (such as the swollen joint count or inflammatory marker) was associated with sustained remission. It may be that improvements in objective measures of disease activity improve more uniformly in response to anti-TNF in the majority of patients, whereas the more subjective components of the disease activity score and patient directed outcome measures (such as the HAQ) are more variable in their response to anti-TNF. The world health organisation international classification of functioning, disability and health (WHO-ICF)(33) recognises the multi-faceted nature of an individual's perception of health, disability and functioning, and may provide some insight as to why there appears to be no association between sustained remission and objective measures of disease activity. In the WHO-ICF model, the actual health condition only accounts for one of six dimensions that contribute to an individual's perception of health and functioning. Participation in life situations, limitations on ability to undertake activities, impairment to body functions, environmental aids or barriers and personal factors all interact in an individual's perception of health. Quantification and reporting quality of life (such as fatigue) is a problem encountered in many chronic conditions and a recent Cochrane review demonstrated modest improvement in fatigue in response to anti-TNF and other biologic therapy (34). However, a cross-sectional evaluation of the British Society for Rheumatology Biologics Registry for RA (BSRBR-RA) investigating fatigue remission identified that only 37% of those individuals who achieved DAS28 remission at 6 months achieved a corresponding remission of their fatigue (35).

All the composite outcome measures included in this review contain components that indirectly measure non-disease dimensions (the global health measure). Personal factors also contribute to a patient's reporting of these subjective components. Therefore, the reduction in inflammatory burden could be offset by a lack of effect on subjective components of the score, which may not be directly related to disease activity. This poses wider questions for the use of composite outcome measures to quantify therapeutic efficacy of a targeted drug such as anti-TNF. Whilst blockade of the TNF pathway reduces joint damage, inflammation and swelling of active RA, it may be that a patient's pain and fatigue is driven by other factors unrelated to their RA. In these cases, classifying the patient as a 'non-responder' to anti-TNF is inappropriate. However, none of the studies identified in this review presented data on possible confounders such as fatigue, so we are unable to comment on the relationship between such factors and sustained remission. A future approach for identifying the impact of non-inflammatory factors in the composite outcome measure may be to measure key quality of life metrics (such as fatigue, mood etc.) at two six monthly intervals prior to addition of anti-TNF therapy, with subsequent regular measurement thereafter. If reductions in objective markers of inflammation are noted, but subjective markers and quality of life measures remain poor, therapies targeted at addressing quality of life factors may be more efficacious in eliciting a favourable outcome than switching RA treatment modality.

Conclusions

Despite the clinical relevance sustained remission remains a poorly reported outcome. Reporting the number of patients in a sustained state of remission or low disease activity, and their clinical features, would not require any additional data collection than currently occurs in most clinical studies, and would greatly assist in assessing the real-world clinical benefit of these treatments to patients. Furthermore, understanding of how individual components of composite outcome measures (such as the DAS28) vary in response to disease modifying treatment is needed in order to appropriately tailor treatment to the individual.

With the increasingly widespread use of anti-TNF therapy, and aspirations of moving towards personalised medicine, understanding which patients achieve the most profound and durable therapeutic effect is essential to ensuring high quality and cost-effective management decisions, as well as considering the wider context in which an individual's disease sits.

Word Count 3608 (Main body of text)

Acknowledgements

This work was conducted on behalf of BSR and the author would like to thank BSR for its help and support

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Table 1. Newcastle-Ottawa Quality Scoring

	Score	Acceptable	<i>Brocq 2009</i>	<i>Furst 2011</i>	<i>Balogh 2013</i>	<i>Barnabe 2014</i>	<i>Einarsson 2015</i>	<i>Tanaka 2015</i>
Selection	Representativeness of the exposed cohort	Truly or somewhat representative of the average RA patient using anti-TNF in the community	Nil	*	Nil	*	*	Nil
	Representativeness of the non-exposed cohort	Drawn from the same community as the exposed cohort	*	*	*	*	*	*
	Ascertainment of exposure	Secure record or structured interview	*	*	*	*	*	*
	Demonstration that the outcome was not present at the start of the study	Documented that patients were not in remission at the time of entry	*	*	*	Nil	Nil	*
Comparability	Comparability of cohorts	Subgroups (exposed and non-exposed) were drawn from the same cohort (2 stars)	**	**	**	**	**	**
Outcome	Assessment of outcome	Independent blind assessment or record linkage	*	*	*	*	*	*
	Was follow-up long enough for outcome to occur	At least 6 months follow-up after the first review following baseline visit	*	*	*	*	*	*
	Adequacy of follow-up	All subjects accounted for or <10% of patients lost to follow-up (unless detailed description that those lost to follow-up would not have introduced bias)	Nil	Nil	*	*	*	*
Summary		Selection (Max 4 *)	***	****	***	***	***	***
		Comparability (Max 2 *)	**	**	**	**	**	**
		Outcome (Max 3 *)	**	**	***	***	***	***

Table 2. Summary of Studies & Baseline Characteristics

Author, year	Country	Study Duration & Design	Sample Size & Gender (Female)	Anti-TNF group inclusion criteria	Co-medication (included/ excluded)	Mean Age & disease duration (yrs)	Disease activity measure	Mean +/- SD disease activity	HAQ score, mean or median +/- SD or (range)	Proportion of Cohort in Sustained Remission (%), Criteria	
Brocq 2009	France	7 years, Retrospective Cohort	304, 81.3% ¹	RA patients with failure of methotrexate and DAS28 \geq 5.1. Previous anti-TNF treatment allowed.	Included Prednisolone (\leq 5mg) Synthetic DMARD (stable dose) Excluded NSAID users	58 ¹ , 10 ¹	DAS28	6.4 ¹	Not given	8.2% DAS28	
Furst 2011	USA	7 years, Prospective Cohort (stratified by disease duration)	3170, 77.4-79.8% (depending on subgroup)	RA patients starting on anti-TNF	Included Synthetic DMARD (dose unspecified) Excluded None specified	54.3, 2.5	DAS28	4.4 \pm 1.4	M-HAQ values 0.5 (mean) \pm 0.5 (SD)	8.9%, DAS28	
							CDAI	21.8 \pm 13.7		9.7%, CDAI	
						54.1, 7.7	DAS28	4.5 \pm 1.5		11.6%, DAS28	
							CDAI	21.0 \pm 13.8		9.5%, CDAI	
						60.5, 20.3	DAS28	4.6 \pm 1.5		4.9%, DAS28	
							CDAI	21.5 \pm 13.1		4.2%, CDAI	
Balogh 2013	Ireland	1 year, Prospective Cohort	273, 74.4%	Biologic naïve RA patients with persistent disease activity starting on anti-TNF	None specified	59.9, 13.4	DAS28, ACR/EULAR	5.33 \pm 1.07	Not given	9.9%, DAS28 (from ACR/EULAR subgroup)	
Barnabe 2014	Canada	7 years, Prospective Cohort	1116, 74.0%	Biologic naïve, RA refractory to parenteral methotrexate/ leflunomide, at least 2 study visits	None specified	54.4, 12.2	DAS28	6.03 \pm 1.30	1.62 (mean), 0.68	21.5%, DAS28	
							CDAI	38.52 \pm 13.59		9.9%, CDAI	
							SDAI	40.90 \pm 14.66		4.5%, SDAI	
							ACR/EULAR 2011 (no CRP)	NA		10.8%, ACR/EULAR 2011 (minus CRP component)	
							ACR/EULAR	NA		6.8%, ACR/EULAR 2011	
Tanaka 2015	Japan	3 years, Open label, non-randomised study	197, 84.8%	RA patients with inadequate response (DAS28-ESR \geq 3.2) to Methotrexate and/or other non-biological DMARDs	Included None specified Excluded Steroid use NSAID and Coxib use Variable synthetic DMARD use	60.7, 8.9	DAS28-ESR	5.4	Not given	38.1%, DAS28-ESR	
Einarsson 2015	Sweden	10 years, Prospective cohort	2416, 77%	RA patients with active disease + \geq 1 failed previous DMARD. Previous biologic allowed.	None specified	56.0, 11.8	DAS28	5.5	1.3 (mean)	15.8%, DAS28	

¹ Data extracted from referenced paper Brocq 2007(36).

Table 3. Predictors of sustained remission

Study (n)	Predictor	Outcome Measure Used	Effect Size	Association with Sustained Remission
Barnabe 2014 (1116)	Baseline Physician Global (High)	DAS28	OR 0.80, 95% CI 0.66–0.99	Negative
	Obesity	ACR/EULAR Boolean (excluding CRP)	OR 0.30, 95% CI 0.10–0.90	
	Tender Joint Count (High)	CDAI	OR 0.96, 95% CI 0.92–1.00	
	Early response to treatment (<16 weeks)	DAS28	OR 1.88, 95% CI 1.27 – 2.78	Positive
Furst 2011 (3179)	Higher baseline disease activity	DAS28	OR 0.37, 95% CI 0.19 – 0.73	Negative
		CDAI	OR 0.57, 95% CI 0.39 – 0.84	
	Disability	CDAI	OR 0.25, 95% CI 0.08 – 0.79	
	Increased disease duration (5-yearly increments)	CDAI (but not by DAS28)	OR 0.85, 95% CI 0.75 – 0.97	
	Age	DAS28 (but not by CDAI)	OR 0.79, 95% CI 0.63 – 1.00	
	Female gender	DAS28 (but not by CDAI)	OR 0.43, 95% CI 0.23 – 0.82	
	Concomitant prednisolone	CDAI (but not by DAS28)	OR 0.69, 95% CI 0.47 – 1.00	
	Prior anti-TNF use	CDAI	OR 0.98, 95% CI, 0.96 – 1.00	Positive
		DAS28	OR 0.72, 95% CI, 0.54 – 0.94	
	Concomitant methotrexate	CDAI	OR 1.55, 95% CI 1.00 – 2.42	
		DAS28	OR 2.83, 95% CI 1.18 – 6.80	
Balogh, 2013 (273)	Tender Joint Count	DAS28 (as a subgroup of ACR/EULAR criteria)	OR 0.910, p 0.031	Negative
	Increasing Age		OR 0.942, p<0.0001	
Tanaka 2015 (197)	Lower Patient Global Score	DAS28-ESR	41.3 vs. 54.9 mm, p=0.0004	Positive
	Shorter disease duration		7.5 vs. 9.6 yrs, p= 0.005	
	Lower baseline HAQ-DI score		0.96 vs. 1.42, p<0.0001	
	Lower baseline ESR		44.1mm/hr vs. 53.0 mm/hr, p=0.0374	
	Lower baseline DAS28-ESR		5.11 vs. 5.70, p=0.005	
Einarsson 2015 (2416)	Female Gender	DAS28	OR 0.57, 95% CI 0.44 – 0.75	Negative
	Higher baseline disease activity		OR 0.62, 95% CI 0.55 – 0.70	
	Earlier calendar year of starting anti-TNF		OR 0.89, 95% CI 0.85 – 0.93	
	Higher HAQ		OR 0.39, 95% CI 0.31 – 0.49	
	Increasing age		OR 0.98, 95% CI 0.97 – 0.99	
	Concomitant Methotrexate	OR 2.02, 95% CI 1.51 – 2.71	Positive	

Supplementary Online Table 1. Medline Search Criteria

Diagnosis (KW.)		Drug (OR, KW.)		Outcome (OR, KW.)
Rheumatoid arthritis (74933)	A N D	Tumor necrosis factors* (2066) Tumor Necrosis factor-alpha* (116033) Antibodies, Monoclonal* (180019) Antibodies, Monoclonal, Humanized* (25271) Antibodies, Monoclonal, Murine-Derived* (9706) Receptors, Tumor Necrosis Factor* (16571) Certolizumab pegol. kw (373) Golimumab. kw (326) Infliximab. kw (8655) CT-P13* (Infliximab biosimilar). kw (3) Adalimumab. kw (3549) Etanercept. kw (4027) Anti-TNF .kw (6196) Tnf.kw (108867) TNFR-Fc fusion protein.kw (4201) Combined hits with OR 328541 Diagnosis AND Drug combined give 10829 hits	A N D	Remission, Spontaneous* (15099) Treatment outcome* (658026) Severity of illness Index* (171810) Reproducibility of Results* (281754) Remission Induction* (32979) Induction Chemotherapy* (5743) Recovery of Function* (34252) Pharmacology, clinical* (2201) Drug evaluation* (80081) Drug utilization* (20410) Evaluation Studies as Topic* (119716) Maintenance Chemotherapy* (1435) Quality of Health Care* (115945) Sustained remission (kw) (930) Maintained remission (kw) (130) Prolonged remission (kw) (611) Responder (kw) (10266) Disease control (kw) (46264) Disease activity (kw) (24636) DAS28 (kw) (1474) Clinical Disease Activity Index (kw) (184) Simplified Disease Activity Index (kw) (128) DAS (kw) (42944) Remission (kw) (109223) Combined above hits with OR 1676984

*Denotes MeSH heading
(kw) denotes keyword

Search Performed using Ovid interface on 4th September 2015

All above articles were searched as keywords- Diagnosis AND Drug AND Outcome gives 3797 hits

Limit to humans, and adolescent, all adult, young adult, middle age, middle aged, all aged, aged- gives 2413 hits

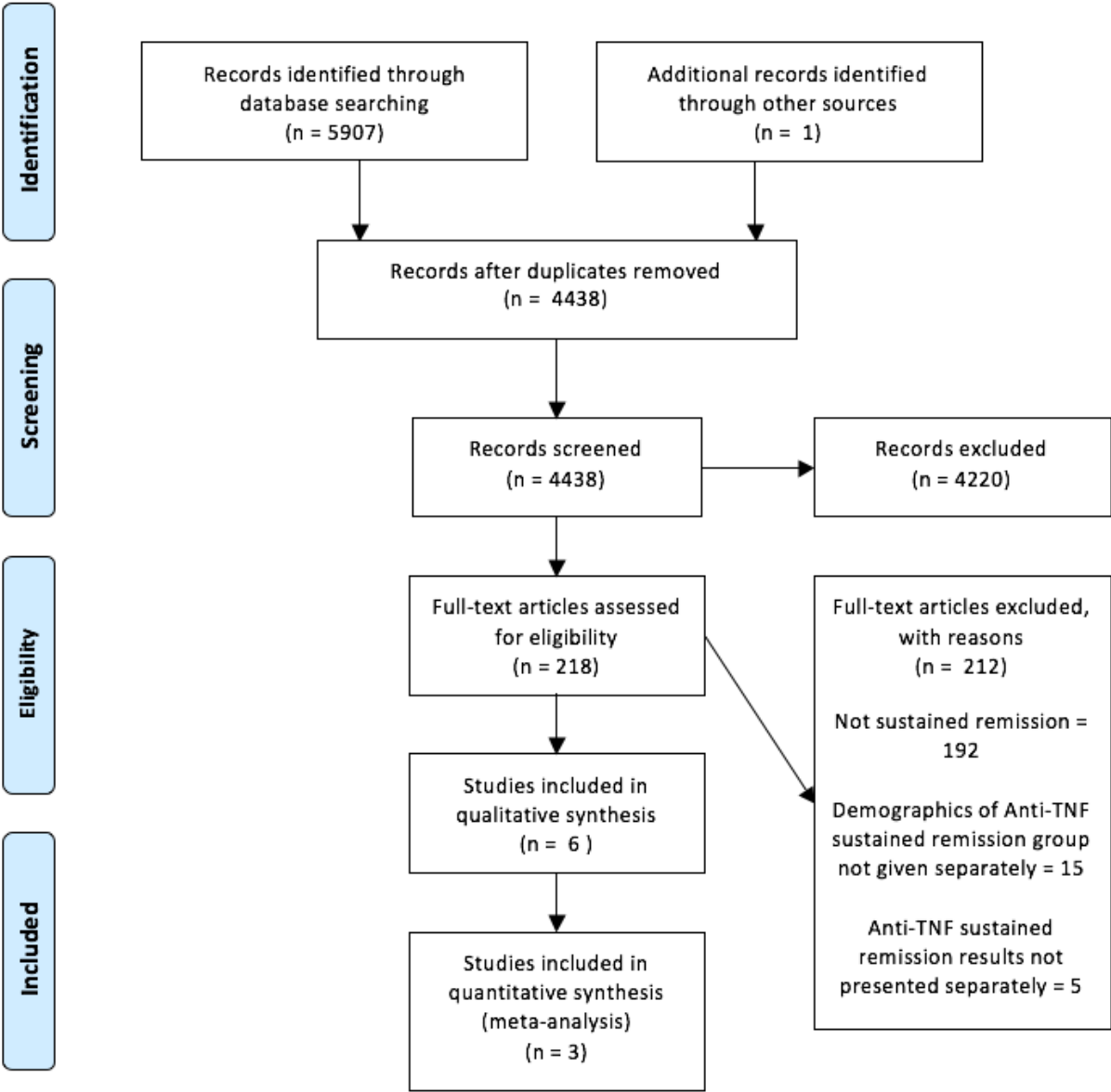


Figure 1. Results of Citation Screening

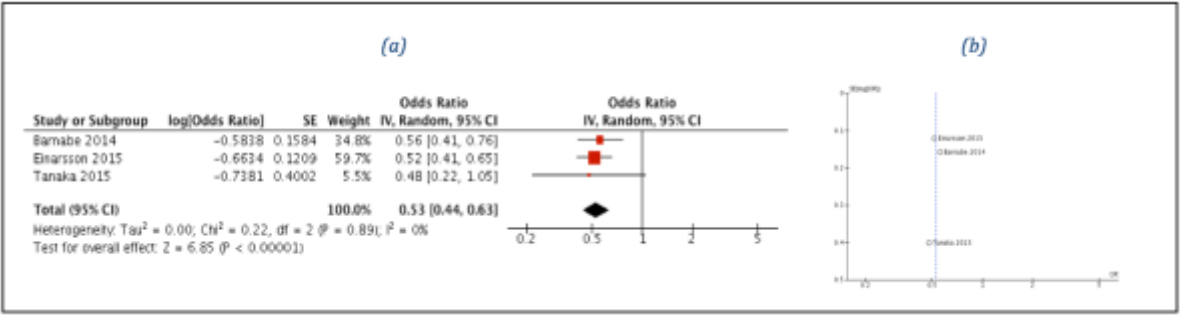


Figure 2. (a) Effect of gender on likelihood of achieving sustained remission and (b) publication bias